HUMAN HEALTH HAZARDS SUMMARY

OVERVIEW: Human health hazards assessment is the process of identifying the potential effects that a chemical may have on humans who are exposed to it, and of determining the levels at which these effects may occur. Exposure to a chemical may occur by inhalation, oral, or dermal routes through the production, use, or disposal of the chemical or products containing the chemical.

GOALS:

- Compile existing information on potential health effects resulting from exposure to a chemical.
- Guide the selection and use of chemicals that pose less risk to humans.
- Assess the potential toxicity of chemicals in a use cluster to humans from available human data, supplementing with animal data when adequate human data are not available.
- Identify the target organ(s) of toxicity by examining the potential effects resulting from acute (short-term) and chronic (long-term) exposure to the chemical by routes pertinent to human exposure.
- Determine if there are levels of concern for the chemical (e.g., the no-observed adverse effect level [NOAEL] and the lowest-observed adverse effect level [LOAEL]), as well as references doses (RfD), carcinogen slope factors (q_1*), and cancer weight-of-evidence classifications.
- Provide the above listed information, including the levels of concern, to the Risk Characterization module.

PEOPLE SKILLS: The following lists the types of skills or knowledge that are needed to complete this module.

- Expertise in evaluating the adverse effects of chemicals on humans, animals, and other biological systems. This requires an understanding of clinical toxicology; procedures and results of standard toxicological test methods; pharmacokinetics, a discipline that includes chemical absorption, distribution, metabolism, and excretion; species differences among experimental animals; the cellular, biochemical, and molecular mechanisms of action of the chemicals; and relationships between chemical structure and toxicity.
- Expertise in analyzing data on adverse effects in human populations (in this case, from exposure to chemicals) and extracting information to identify possible causes. This

discipline requires knowledge of standard protocols for epidemiological studies; demographics; risk factors (e.g., smoking, alcohol consumption, race, sex, obesity, etc.); formal logic; and statistics.

- Expertise in the collection, organization, and interpretation of numerical data; especially the analysis of population characteristics by inference from sampling. This requires knowledge of population parameter estimation (involves a quantitative measure of some property of a sample), hypothesis testing (involves determining if differences in sample statistics [e.g., means] are of sufficient magnitude to distinguish differences between population parameters), and modeling.

Note: The analysis presented in this module should not be undertaken without the assistance of someone with expertise in human health hazards assessment. Furthermore, peer-review of the completed hazard summary is recommended.

DEFINITION OF TERMS: Sources for the following definitions include Alderson, UNDATED ("Epidemiological Method"); Amdur, et. al., 1991 (*Casarett and Doull's Toxicology*); ATSDR, UNDATED (*Toxicological Profile Glossary)*; EPA, 1986a ("Guidelines for Estimating Exposures"); EPA, 1986b (*EPA Toxicology Handbook*); EPA, 1988a ("Part II. Proposed Guidelines for Assessing Female Reproductive Risk"); EPA, 1988b ("Part III. Proposed Guidelines for Assessing Male Reproductive Risk"); EPA, 1991b ("Guidelines for Developmental Toxicity Risk Assessment"); EPA, 1994e (HEAST); EPA, 1995d (IRIS® glossary); Hodgson, et. al., 1988 (*Dictionary of Toxicology)*; Huntsberger and Leaverton, 1970 (*Statistical Inference in Biomedical Sciences*); Lilienfeld and Lilienfeld, 1988 (*Foundations of Epidemiology)*; Norell, 1992 (*A Short Course in Epidemiology)*; and Dorland, 1994 (*Dorland's Illustrated Medical Dictionary*).

Acute Toxicity: Immediate toxicity. Its former use was associated with toxic effects that were severe (e.g., mortality) in contrast to the term "subacute toxicity" that was associated with toxic effects that were less severe. The term "acute toxicity" is often confused with that of acute exposure.

Association: In a formal, scientific context, a statistical relationship between a disease or adverse effect and biological or social characteristics.

Carcinogenicity: The ability of an agent to induce a cancer response.

Chronic Toxicity: Delayed toxicity. However, the term "chronic toxicity" also refers to effects that persist over a long period of time whether or not they occur immediately or are delayed. The term "chronic toxicity" is often confused with that of chronic exposure.

Confounder (Confounding Variable, Factor): A factor that is covariant with the studied exposure in the study base and masks the ability to distinguish the risk of developing the studied disease occasioned by any association between exposure and disease.

Developmental Toxicity: Adverse effects produced prior to conception, during pregnancy, and during childhood. Exposure to agents affecting development can result in any one or more of the following manifestations of developmental toxicity: death, structural abnormality, growth alteration, and/or functional deficit. These manifestations encompass a wide array of adverse developmental end points, such as spontaneous abortion, stillbirths, malformations, early postnatal mortality, reduced birth weight, mental retardation, sensory loss and other adverse functional or physical changes that are manifested postnatally.

Dose-Response: The relationship between the amount of an agent (either administered, absorbed, or believed to be effective) and changes in certain aspects of the biological system (usually adverse effects), apparently in response to that agent.

Exposure Level: In general, a measure of the magnitude of exposure, or the amount of an agent available at the exchange boundaries (i.e., lungs, gastrointestinal tract, or skin), during some specified time. In the Exposure Assessment and Risk Characterization modules, "exposure level" is used specifically as a measure of exposure expressed as a concentration rather than as a potential dose rate.

Extrapolation: An estimation of a numerical value of an empirical (measured) function at a point outside the range of data which were used to calibrate the function. For example, the quantitative risk estimates for carcinogens (according to EPA guidelines at the time of this writing) are generally low-dose extrapolations based on observations made at higher doses. Another example is extrapolation of health effects from occupational to general exposure levels.

Human Equivalent Concentration (HEC): The human exposure concentration of an agent that is believed to induce the same magnitude of toxic effect as that which a known animal or occupational exposure concentration has induced. For HEC, the exposure concentration has been adjusted for dosimetric differences between experimental animal species and humans. If occupational human exposures are used for extrapolation, the human equivalent concentration represents the equivalent human exposure concentration adjusted to a continuous basis.

International Agency for Research on Cancer (IARC) Classification: A method for evaluating the strength of evidence supporting a potential human carcinogenicity judgment based on human data, animal data, and other supporting data. A summary of the IARC carcinogenicity classification system includes:

- Group 1: Carcinogenic to humans.
- Group 2A: Probably carcinogenic to humans.
- Group 2B: Possibly carcinogenic to humans.
- Group 3: Not classifiable as to human carcinogenicity.
- Group 4: Probably not carcinogenic to humans.

Irritation: An inflammatory response, usually of skin, eye, or respiratory tract, induced by direct action of an agent.

LC_{50} (Lethal Concentration): The concentration of a chemical in air that causes death in 50 percent of the test organisms at the end of the specified exposure period. LC_{50} values typically represent acute exposure periods, usually 48 or 96 hours. Typical units are mg/m^3 or ppm.

LD_{50} (Lethal Dose): The dose of a chemical taken by mouth, absorbed by the skin, or injected that is estimated to cause death in 50 percent of the test animals.

Lowest-Observed Adverse Effect Level (LOAEL): The lowest dose level in a toxicity test at which there are statistically or biologically significant increases in frequency or severity of adverse effects in the exposed population over its appropriate control group.

Modifying Factor (MF): An uncertainty factor that is greater than zero and less than or equal to 10; the magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and data base not explicitly treated with the standard uncertainty factors (e.g., the completeness of the overall data base and the number of species tested); the default MF is 1.

Mutagen: An agent that produces a permanent genetic change in a cell (other than changes that occur during normal genetic recombination).

Neurotoxicity: Any toxic effect on any aspect of the central or peripheral nervous system. Such changes can be expressed as functional changes (such as behavioral or neurological abnormalities) or as neurochemical, biochemical, physiological or morphological perturbations.

No-Observed Adverse Effect Level (NOAEL): The highest dose level in a toxicity test at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects in the exposed population over its appropriate control; some effects may be produced at this level, but they are not considered adverse, nor precursors to adverse effects.

Odds Ratio (OR): A technique for estimating the relative risk (see below) from case-control (retrospective) studies. This refers to the odds, among diseased individuals, of being exposed as compared to non-diseased individuals.

Pharmacokinetics: The dynamic behavior of chemicals within biological systems. Pharmacokinetic processes include uptake, distribution, metabolism, and excretion of chemicals.

Proportionate Mortality Ratio (PMR): The number of deaths from a specific cause and in a specific period of time per 100 deaths in the same time period.

q_1^*: See Slope Factor.

Reference Concentration (RfC): An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime. RfCs are generally reported as a concentration in air (mg/m^3).

Reference Dose (RfD): An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime. RfDs are reported as mg/kg-day.

Reportable Quantity (RQ): The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are: (1) one pound; or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity: The occurrence of effects on the male or female reproductive system that may result from exposure to environmental agents. The manifestations of such toxicity may include alteration in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of the reproductive system.

Risk: In general, risk pertains to the probability and severity of adverse effects (e.g., injury, disease, or death) under specific circumstances. In the context of a CTSA, risk is an expression of the likelihood of adverse health or environmental effects from a specific level of exposure; only cancer risk is estimated as a probability.

Risk Assessment: The determination of the kind and degree of hazard posed by an agent, the extent to which a particular group of people has been or may be exposed to the agent, and the present or potential health risk that exists due to the agent.

Risk Characterization: The integration of hazard and exposure information to quantitatively or qualitatively assess risk. Risk characterization typically includes a description of the assumptions, scientific judgments, and uncertainties that are part of this process.

Slope Factor (q_1*): A measure of an individual's excess risk or increased likelihood of developing cancer if exposed to a chemical. It is determined from the upperbound of the slope of the dose-response curve in the low-dose region of the curve. More specifically, q_1* is an approximation of the upper bound of the slope when using the linearized multistage procedure at low doses. The units of the slope factor are usually expressed as 1/(mg/kg-day) or $(mg/kg\text{-}day)^{-1}$.

Standardized Mortality Ratio (SMR): The ratio of observed events to events expected if the age- and sex-specific mortality rates of a standard population (usually the general population) are applied to the population under study.

Structure Activity Relationship (SAR): The relationship of the molecular structure and/or functional groups of a chemical with specific effects. SARs evaluate the molecular structure of a chemical and make qualitative or quantitative correlations of particular molecular structures and/or functional groups with specific effects.

Subchronic Exposure: Multiple or continuous exposures occurring usually over 3 months. This applies to animal, not human, exposure.

Subchronic Toxicity: Effects from subchronic exposure. This also applies to animal, not human exposure.

Uncertainty Factor (UF): One of several, generally 10-fold factors, used in operationally deriving the RfD or RfC from experimental data. UFs are intended to account for: (1) the variation in sensitivity among the members of the human population; (2) the uncertainty in extrapolating animal data to the case of humans; (3) the uncertainty in extrapolating from data obtained in a study that is of less-than-lifetime exposure; and (4) the uncertainty in using LOAEL data rather than NOAEL data.

Unit Risk: The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 µg/L in water or 1 $\mu g/m^3$ in air (with units of risk per $\mu g/m^3$ air or risk per µg/L water).

Upper Bound: An estimate of the plausible upper limit to the true value of the quantity. This is usually not a statistical confidence limit unless identified as such explicitly, together with a confidence level.

Weight-of-Evidence Classification (EPA): In assessing the carcinogenic potential of a chemical, EPA classifies the chemical into one of the following groups, according to the weight-of-evidence from epidemiologic and animal studies:

- Group A: Human Carcinogen (sufficient evidence of carcinogenicity in humans).
- Group B: Probable Human Carcinogen (B1 - limited evidence of carcinogenicity in humans; B2 - sufficient evidence of carcinogenicity in animals with inadequate or lack of evidence in humans).
- Group C: Possible Human Carcinogen (limited evidence of carcinogenicity in animals and inadequate or lack of human data).
- Group D: Not Classifiable as to Human Carcinogenicity (inadequate or no evidence).
- Group E: Evidence of Noncarcinogenicity for Humans (no evidence of carcinogenicity in adequate studies).

(The "Proposed Guidelines for Carcinogen Risk Assessment" [EPA, 1996b] propose use of weight-of-evidence descriptors, such as "Likely" or "Known," "Cannot be determined," and "Not likely," in combination with a hazard narrative, to characterize a chemical's human carcinogenic potential - rather than the classification system described above.)

ADDITIONAL TERMS: The following additional terms are not used in this module discussion *per se*, but are likely to be found in the literature pertaining to human health hazard and toxicity studies.

Acute Exposure: Exposure occurring over a short period of time. (The specific time period varies depending on the test method and test organism or the receptor of interest.)

Case-Control Study: An epidemiological study in which comparisons are made between a group of persons who have a disease (cases) and a group who do not (controls) regarding possible exposures prior to study.

Case Report: An anecdotal description of the occurrence of a disease or adverse effect in an individual or group of individuals.

Case Study: A detailed analysis of an individual or group.

Chronic Exposure: Continuous or intermittent exposure occurring over an extended period of time, or a significant fraction of the animal's or the individual's lifetime.

Cohort Study: Epidemiological study comparing the morbidity and/or mortality of a group or groups of people (called exposed) who have had a common insult (e.g., exposure to a chemical suspected of causing disease) with a group believed to be unexposed or with the general population.

Correlation: The degree to which two or more phenomena occur together or vary in similar directions.

Cross-Sectional Study: An epidemiological study in which comparisons are made between a group of persons who are found to have an exposure and a group who does not (unexposed). The characteristics under comparison are present in both exposed and unexposed groups at the time of the study and exposure status is often determined after individuals are selected for study. Also called a "prevalence" study.

EPA Health Advisory: An estimate of acceptable drinking water levels for a chemical, based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Human Equivalent Concentration (HEC): See definition for Human Equivalent Dose.

Human Equivalent Dose (HED): The human dose of an agent that is believed to induce the same magnitude of toxic effect as that which a known animal or occupational dose has induced. For HEC, the dose has been adjusted for dosimetric differences between experimental animal species and humans. If occupational human exposures are used for extrapolation, the HED represents the equivalent human exposure concentration adjusted to a continuous basis.

Irreversible Effect: Effect characterized by the inability of the body to partially or fully repair injury caused by a toxic agent.

Latency Period: The time between the initial induction of a health effect and the manifestation (or detection) of the health effect; crudely estimated as the time (or some fraction of the time) from first exposure to detection of the effect.

Potentiation: The ability of one chemical to increase the effect of another.

Prevalence Study: An epidemiological study that examines the relationship between exposure and diseases as they exist at a given period in time. (See also Cross-Sectional Study.)

Prospective Study: A study using a population sample based on exposure status, where exposure may be related to the development of the disease under investigation. The individuals are then followed for several years to see which ones develop and/or die from the disease. Also described by the terms "cohort," "incidence," and "longitudinal." When based on exposure status determined from some time in the past, this may be called "historical prospective."

Relative Risk: The likelihood that an exposed individual will have a disease expressed as a multiple of the likelihood among unexposed (with disease incidence expressed as incidence rate or cumulative incidence).

Retrospective Study: Epidemiological study in which comparisons are made between a group of persons who have a disease (cases) and a group who do not (controls). An attempt is made to determine whether the characteristics (e.g., exposure to a chemical) were present in the past. Also described as "case control," or "case history" studies.

Reversible Effect: An effect that is not permanent, particularly an adverse effect that diminishes when exposure to a toxic chemical ceases.

Spurious Association: A statistical association that represents a statistical artifact or bias. It may arise from biased methods of selecting cases and controls, recording observations or by obtaining information by interview, and cannot be identified with certainty.

Statistical Tests of Significance: Methods for determining on a probabilistic basis if differences in groups under treatment (or observation) could have resulted by chance, or if they represent "rare" events. Also called "statistical tests of hypotheses." The question of random occurrence may be put in the form of a hypothesis to be tested, called the "null hypothesis."

Subacute Exposure: A term, no longer commonly used, that denotes exposures that are longer than acute and shorter than subchronic.

Subacute Toxicity: Effects from subacute exposure.

Subclinical Toxicity: An observable effect which may or may not have any clinical significance (i.e., not biologically significant). With humans it may also mean that the individual's illness is undetected.

Toxicity Assessment: Characterization of the toxicological properties and effects of a chemical, including all aspects of its absorption, metabolism, excretion and mechanism of action, with special emphasis on the identification of a dose-response relationship.

Transient Effect: An effect that disappears over time (irrespective of whether or not exposure continues).

APPROACH/METHODOLOGY: The following presents a summary of the technical approach or methodology for preparing a summary human health hazards profile for a CTSA. Further details for Steps 4 through 8 are presented in the next section of this module.

Step 1: Obtain the CAS RN, synonyms, and information on the chemical structure from the Chemical Properties module.

Step 2: Review the Environmental Fate Summary module to determine if the chemical persists long enough in any environmental medium to be a potential health hazard and if any chemical degradation products need to be considered.

Step 3: Review preliminary exposure pathways from the Exposure Assessment module, if available. The main routes to consider are oral, inhalation, and dermal.

Step 4: Obtain peer-reviewed literature, beginning with secondary sources (e.g., EPA's Integrated Risk Information System [IRIS], EPA review documents, Agency for Toxic Substance and Disease Registry [ATSDR] Profiles, and the Hazardous Substances Data Bank [HSDB]). Resort to primary sources (e.g., journal articles) only when secondary sources are lacking or when more recent information is available in the primary literature that adds new information to the data base for that chemical.

This should include a review of the pharmacokinetics of the chemical and an evaluation of the following toxicological endpoints for both humans and animals:

- Acute toxicity.
- Irritation/sensitization.
- Neurotoxicity.
- Subchronic/chronic toxicity (includes systems such as renal, hepatic, hematopoietic, etc.).
- Developmental/reproductive toxicity.
- Genotoxicity.
- Carcinogenicity.

Step 5: Review the acquired literature and critically evaluate the quality of studies (e.g., use of controls, appropriate numbers of animals, selection of appropriate human study groups, statistical analysis of the data).

Step 6: Construct a health hazards profile for each chemical using the most recent data available. Measured data should take precedence over modeled data. Toxicity summaries should include NOAELs, LOAELs, and RfDs or RfCs for chemicals not causing cancer; and q_1*, unit risk values, and weight-of-evidence classifications for carcinogens. Secondary sources that may contain these types of data are listed in Table 5-11: Sources of Human Health Hazard Data.

Note: Data requirements for toxicity summaries may change as EPA guidance is updated, e.g., changes in the proposed carcinogen risk assessment guidelines (EPA, 1996b).

Present the data clearly and accurately, using consistent units so that comparisons may be easily made. Use the original dose units as well as converted units where possible. Note any assumptions made in dose conversions. Explicitly identify any data that are not peer-reviewed.

Step 7: If some chemicals do not have the values listed in Step 6 and if the necessary data are available, RfDs, carcinogenicity slope factors, and unit risk values or other measures may be calculated. See Details: Step 7 (below), and Table 5-10: Published Guidance on Health Hazards Assessment.

Step 8: In a tabular format, list the toxicity values and classifications that are described in Step 6 (see Details: Step 8, below) and provide to the Risk Characterization module.

METHODOLOGY DETAILS: This section presents methodology details for completing Steps 4 through 8. If necessary, additional information on these and other steps can be found in the previously published guidance (see Table 5-10: Published Guidance on Health Hazards Assessment).

Details: Step 4, Obtaining Literature Information

In vitro studies are useful for mutagenicity assays and for determining structure-activity relationships and mechanisms of toxicity. Note that because of the importance of the various manifestations of neurotoxicity, EPA places these effects in a separate section, rather than under acute or chronic/subchronic toxicity, which could also be appropriate.

Toxicity values that are important for risk characterization include, but are not limited to, the following:

- LD_{50} values for mammalian species.
- Concentrations of the chemical that cause irritation to the eyes, nose, or respiratory passages.
- Concentrations or doses that result in acute neurotoxicity; NOAEL and/or LOAEL for subchronic/chronic neurotoxicity.

- NOAEL and/or LOAEL for subchronic/chronic non-carcinogenic systemic effects. If an RfD is available, inclusion of the experimental details of the key study used to derive that value is required.
- NOAEL or LOAEL for developmental/reproductive toxicity. Note that RfDs may be based on developmental or reproductive effects.
- Epidemiological or animal bioassay data for carcinogenicity. This would include q_1* and unit risk values, if available. The EPA, National Toxicology Program, and IARC classify chemicals as to their carcinogenicity. These classifications should be included when available. (Note that epidemiological data may be available for other adverse effects such as developmental or reproductive effects.)
- Regulatory standards and guidelines (e.g., RfDs and RfCs; Occupational Safety and Health Administration [OSHA], American Conference of Governmental Industrial Hygienists, Inc. [ACGIH], and National Institute for Occupational Safety and Health [NIOSH] exposure limits; drinking water standards; and drinking water health advisories).

Details: Step 5, Evaluating Data Quality

Statistics are used to evaluate the magnitude of response in a study and to determine if an effect is the result of exposure to a chemical. If statistics have not been performed on a particular study, and if there are data for more than one dose, one possible protocol would be to first test for a trend. If there is no trend, then determine if any dose group shows an increase or decrease relative to controls. If data are quantal proportions, some form of categorical analysis is appropriate.

Commonly used statistical tests include analysis of variance and Bartlett's tests for homogeneity (for endpoints such as organ and body weights, hematology, and biochemistry); Dunnett's multiple comparison tables (for significance of differences); and life table test, incidental tumor test, Fisher's exact test, and Cochran-Armitage trend test (for analysis of tumor incidence data). Statistical methods are described in references listed in Table 5-10. A statistician and a health hazard assessment expert should be consulted for information regarding when and how these tests are used and whether they are appropriate for the data in hand. It is generally not necessary to perform statistics on data from HSDB, NIOSH, ATSDR, IRIS or other references listed under Sources of Human Health Hazards Data in Table 5-11.

Details: Step 6, Constructing the Health Hazards Profile

The level of detail presented in the health hazards profile may vary. For example, key studies (such as those used in the derivation of toxicity values such as chronic RfDs, RQs, or carcinogenicity slope factors) require more detailed reporting than supporting studies. A detailed, but concise, description would include experimental details and incidence data for effects, relating exposure and effect. Supporting studies may be described with fewer details and, where appropriate, as ranges of values. Adequate citations should be provided for both key and supporting studies. When epidemiological data are available, epidemiological summaries

should include population observed, comparison population, SMRs, PMRs, or ORs and confounding factors.

The health hazards profile for discrete organic chemicals can be constructed using concentrations or doses derived from experimental studies or can be estimated from structure activity relationships (SARs; see next paragraph). The toxicity of inorganic chemicals typically cannot be accurately estimated using SARs. The hazard profile for inorganic chemicals should therefore be constructed using effective concentrations based on measured toxicity test data. If no data are available, actual data from the nearest structural analog can be used. Chemical mixtures such as petroleum products (i.e., mineral spirits or solvent naphtha) may be evaluated from information on the mixture, information from a "sufficiently similar" mixture, or information on the individual components of the mixture. Constructing a Health Hazard Profile for chemical mixtures is a complex process and the EPA "Guidelines for the Health Risk Assessment of Chemical Mixtures" should be consulted (see published guidance listed in Table 5-10).

When measured data are not available, evaluate data from studies on structurally-related compounds. The use, application, development, and validation of SARs have been discussed in a number of publications (see *Federal Register* citations in Table 5-10). The use and interpretation of SARs require expertise and caution. Computer models that calculate toxicity values based on SARs are available (see Table 5-9: Computer Programs Used in Human Health Hazards Assessment). Briefly, the EPA approach to SARs involves the evaluation and interpretation of available and pertinent data on the chemical under study or its potential metabolites; evaluation of test data on analogous substances and potential metabolites; and the use of mathematical expressions for biological activity or quantitative structure activity relationships (QSARs).

Details: Step 7, Deriving Health Hazard Values

Reference Dose/Reference Concentration (RfD/RfC)

RfDs and RfCs are derived following a thorough examination of the toxicologic and epidemiologic literature for the subject chemical and selection of the studies that are judged to be appropriate for risk assessment. The LOAEL or NOAEL (chronic, subchronic, developmental, or reproductive toxicity) is divided by uncertainty factors and a modifying factor to derive the RfD. If a study has more than one NOAEL, the highest is selected. If there is no NOAEL the RfD may be derived from a LOAEL by applying an uncertainty factor of up to 10. The lowest of the LOAELs for systemic, developmental, or reproductive toxicity is chosen.

The RfD is calculated as follows:

$$\text{RfD} = \frac{\text{NOAEL (mg/kg-day)}}{\text{UFs x MF}}$$

where:

NOAEL = No-observed adverse effect level
UFs = Uncertainty factors
MF = Modifying factor (see Definition of Terms)

Ufs account for the following:

- The variation in sensitivity among the members of the human population (a factor of 10).
- The extrapolation of animal data to humans (a factor of 10).
- Extrapolation from less than lifetime exposure (a factor of 10).
- The use of LOAEL, rather than NOAEL, data (a factor of 10).
- Extrapolation from experimental data that do not fully consider all possible adverse effects (a factor of from 1 to 10).

The methodology for the inhalation RfC includes dosimetric adjustments to account for the species-specific relationships of exposure concentrations to deposited/delivered doses. This requires knowledge of the anatomy and physiology of the lungs and airways to accurately estimate the amount of the inhaled chemical that would reach the tissue where the effects occur. The RfC is calculated similarly to RfD, as follows:

$$RfC = \frac{NOAEL_{[HEC]}\ (mg/m^3)}{UFs \times MF}$$

where:

$NOAEL_{[HEC]}$ = the NOAEL or equivalent effect level dosimetrically adjusted to a human equivalent concentration (HEC)

Slope Factor

The slope factor is a measure of the incremental risk or increased likelihood of an individual developing cancer if exposed to a unit dose of the chemical for a lifetime. The risk is expressed as a probability (i.e., one chance in ten or one chance in one million), and the unit dose is normally expressed as 1 mg of the chemical per unit body weight (kg) per day:

Slope Factor = Risk per unit dose, or Risk per mg/kg-day

When based on animal data, the slope factor is derived by extrapolating from the incidences of tumors occurring in animals receiving high doses of the chemical to low exposure levels expected for human contact in the environment. The EPA uses q_1* for its risk assessments (see definition of slope factor). The q_1* for a chemical, in units of $(mg/kg\text{-}day)^{-1}$, is based on the linearized multistage procedure for carcinogenesis and can be calculated by computer program (e.g., GLOBAL).

Slope factor or q_1* values are used in the Risk Characterization module to estimate cancer risk (in the range where it is expected to be linearly related to exposure). It should be noted that the

proposed carcinogen risk assessment guidelines (EPA, 1996b), if adopted, may require modifications to this approach.

Unit Risk

The slope factor, or q_1*, can also be used to determine the incremental cancer risk that would occur if the chemical was present in an environmental medium such as drinking water at a unit concentration (i.e., 1 μg of chemical per liter of drinking water). The calculation for drinking water usually assumes the person weighs 70 kg and drinks 2 liters of water per day:

$$\text{Drinking Water Unit Risk} = q_1^* \times 1/70 \text{ kg} \times 2 \text{ L/day} \times 10^{-3}$$

Air unit risk (risk per µg/m^3) is derived from the linearized multistage procedure and calculated using the GLOBAL program.

Details: Step 8, Tabulating Toxicity Values

Table 5-8 is an example format for tabulating toxicity values.

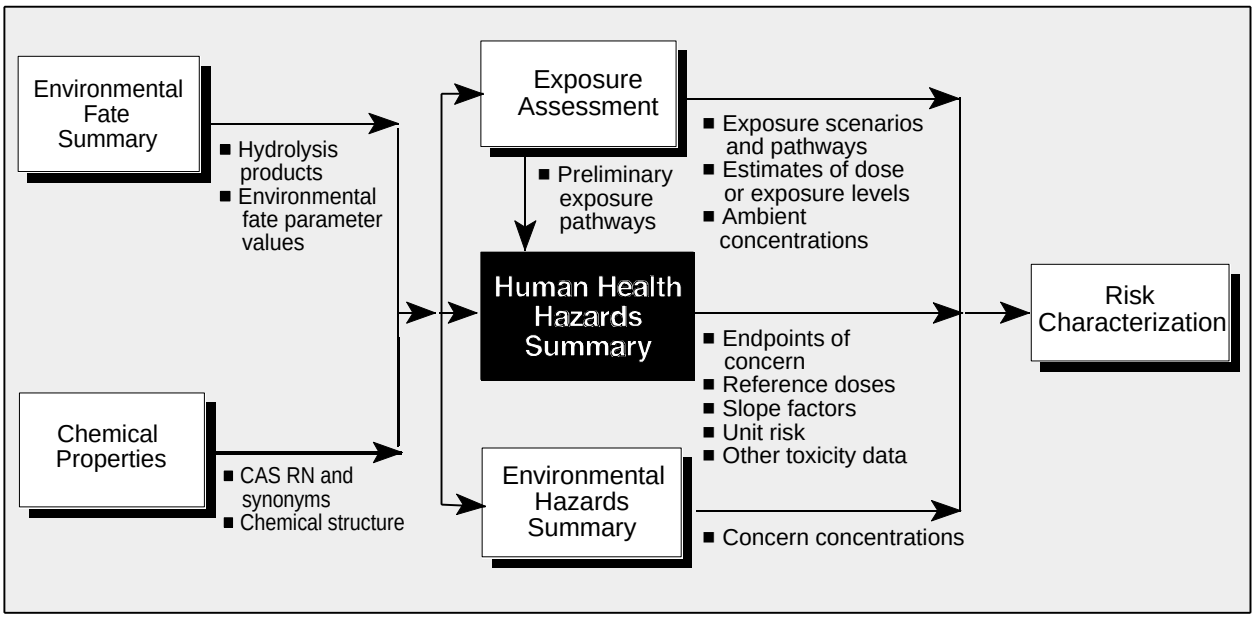
TABLE 5-8: SUMMARY TABLE FOR TOXICITY OF CHEMICALS AND POTENTIAL SUBSTITUTES

Chemical	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10
LD_{50}/LC_{50}										
Irritation (yes or no)										
1. eye	1.	1.	1.	1.	1.	1.	1.	1.	1.	1.
2. skin	2.	2.	2.	2.	2.	2.	2.	2.	2.	2.
3. respiratory	3.	3.	3.	3.	3.	3.	3.	3.	3.	3.
Sensitization (yes or no)										
Neurotoxicity (yes or no)										
Developmental Toxicity (yes or no)										
NOAEL/LOAEL[a] (target organ or effect)										
RfD/RfC										
EPA WOE[b]										
Oral Slope Factor $(mg/kg\text{-}day)^{-1}$										
Unit Risk										
1. air (risk per µg/m^3)	1.	1.	1.	1.	1.	1.	1.	1.	1.	1.
2. water (risk per µg/L)	2.	2.	2.	2.	2.	2.	2.	2.	2.	2.
Exposure Limits										
1. ACGIH	1.	1.	1.	1.	1.	1.	1.	1.	1.	1.
2. OSHA	2.	2.	2.	2.	2.	2.	2.	2.	2.	2.
3. NIOSH	3.	3.	3.	3.	3.	3.	3.	3.	3.	3.

a) If more than one NOAEL select the highest; if no NOAEL, but more than one LOAEL, select the lowest. Include NOAEL/LOAELs for neurotoxicity and developmental toxicity, if available.
b) WOE = weight-of-evidence classification for carcinogenicity.

FLOW OF INFORMATION: This module receives information from the Chemical Properties, Environmental Fate Summary, and Exposure Assessment modules, and transfers information to the Risk Characterization module. Example information flows are shown in Figure 5-5. This module can also be used alone to guide the selection and use of chemicals that are less toxic to humans.

FIGURE 5-5: HUMAN HEALTH HAZARDS SUMMARY MODULE: EXAMPLE INFORMATION FLOWS



ANALYTICAL MODELS: Table 5-9 presents references of computer programs that can be used when estimating toxicity reference values.

TABLE 5-9: COMPUTER PROGRAMS USED IN HUMAN HEALTH HAZARDS ASSESSMENT

Reference	Type of Model
GLOBAL92 ICF Kaiser International, Inc.	A program which uses quantal cancer dose-response animal bioassay data to predict the probability of a specific health effect by fitting a specific form of mathematical model to the data provided.

TABLE 5-9: COMPUTER PROGRAMS USED IN HUMAN HEALTH HAZARDS ASSESSMENT	
Reference	**Type of Model**
QSAR: A Structure-Activity Based Chemical Modeling and Information System. 1986.	Modified structure-activity correlations are used to estimate chemical properties, behavior, and toxicity. Developed by U.S. EPA, Environmental Research Laboratory, Duluth, MN, Montana State University Center for Data Systems and Analysis, and Pomona College Medicinal Chemistry Project.
RISK81 Contact Daniel Krewski Health and Welfare Canada	For low-dose extrapolation of quantal response toxicity data.
TOXRISK Crump, K., et. al. 1995.	Software package for performing standard types of health risk assessments. Provides some quantal and time-to-tumor models.

Note: References are listed in shortened format, with complete references given in the reference list following Chapter 10.

PUBLISHED GUIDANCE: Table 5-10 presents references for published guidance on health hazard assessment.

TABLE 5-10: PUBLISHED GUIDANCE ON HEALTH HAZARDS ASSESSMENT	
Reference	**Type of Guidance**
Abramson, J.H. 1988. *Making Sense of Data: A Self-Instruction Manual*.	Interpretation of epidemiological data.
Armitage, P. and G. Berry. 1994. *Statistical Methods in Medical Research*.	Methods for statistical analysis.
Barnes, D.G. and M. Dourson. 1988. "Reference Dose (RfD): Description and Use in Health Risk Assessments."	Condensed description of RfD derivation.
Breslow, N.E. and N.E. Day. 1980. *Statistical Methods in Cancer Research. Vol. I: The Analysis of Case-control Studies*.	Methods for the statistical analysis of epidemiological studies.
Breslow, N.E. and N.E. Day. 1987. *Statistical Methods in Cancer Research. Vol. II: The Analysis of Cohort Studies*.	Methods for the statistical modeling of epidemiological studies.
Clayton, D. and M. Hills. 1993. *Statistical Models in Epidemiology*.	Methods for the statistical modeling of epidemiological studies.

TABLE 5-10: PUBLISHED GUIDANCE ON HEALTH HAZARDS ASSESSMENT

Reference	Type of Guidance
Gad, S.D. and C.S. Weil, Eds. 1986. *Statistics and Experimental Design for Toxicologists*.	Methods for statistical analysis.
Gart, J.J., et. al. 1986. *Statistical Methods in Cancer Research. Vol. III: The Analysis of Long-term Animal Experiments.*	Methods for the statistical analysis of chronic animal studies.
O'Bryan, T.R. and R.H. Ross. 1988. "Chemical Scoring System for Hazard and Exposure Identification."	Ranking system for 11 parameters, including acute and chronic toxicity.
Snedecor, G.W. and W.G. Cochran. 1980. *Statistical Methods*.	General statistical methods.
U.S. Environmental Protection Agency. 1984a. *Methodology and Guidelines for Ranking Chemicals Based on Chronic Toxicity Data*.	Describes derivation of reportable quantity (RQ); incorporates a 10-point severity ranking system for the chronic toxicity of chemicals that can be used in risk characterization.
U.S. Environmental Protection Agency. 1985. *Toxic Substances Control Act Test Guidelines: Final Rules*.	Describes guidelines for performing tests of chemical fate and environmental and health effects.
U.S. Environmental Protection Agency. 1986c. "Guidelines for Carcinogen Risk Assessment."	Describes procedure for the performance of risk assessment on potential chemical carcinogens. (Soon to be revised.)
U.S. Environmental Protection Agency. 1986d. "Guidelines for Mutagenicity Risk Assessment."	Describes procedure for the performance of risk assessment on potential chemical mutagens.
U.S. Environmental Protection Agency. 1986e. "Guidelines for the Health Risk Assessment of Chemical Mixtures."	Describes procedure for the performance of risk assessment on mixtures of chemicals.
U.S. Environmental Protection Agency. 1988a. "Part II. Proposed Guidelines for Assessing Female Reproductive Risk and Request for Comments."	Proposed guidelines for the evaluation of potential toxicity of environmental agents to the human female reproductive system. Provides discussion of female reproductive organs and their functions, endpoints of toxicity in animal assays, human studies, and risk assessment.
U.S. Environmental Protection Agency. 1988b. "Part III. Proposed Guidelines for Assessing Male Reproductive Risk and Request for Comments."	Proposed guidelines for the evaluation of potential toxicity of environmental agents to the human male reproductive system. Provides discussion of male reproductive organs and their functions, endpoints of toxicity in animal assays, human studies, and risk assessment.

TABLE 5-10: PUBLISHED GUIDANCE ON HEALTH HAZARDS ASSESSMENT	
Reference	**Type of Guidance**
U.S. Environmental Protection Agency. 1989a. *Risk Assessment Guidance for Superfund. Volume I. Human Health Evaluation Manual (Part A).*	Guidance for developing human health risk assessments at Superfund sites.
U.S. Environmental Protection Agency. 1991b. "Guidelines for Developmental Toxicity Risk Assessment."	Discusses basics of developmental toxicity and EPA's risk assessment process for developmental toxins.
U.S. Environmental Protection Agency. 1991c. *General Quantitative Risk Assessment Guidelines for Noncancer Health Effects*.	Discusses various aspects of risk assessment (hazard identification, dose-response assessment, risk characterization). A draft document to be used as guidance; not necessarily Agency policy at present.
U.S. Environmental Protection Agency. 1992a. "Guidelines for Exposure Assessment."	Provides a general approach and framework for carrying out human or nonhuman exposure assessments for specified pollutants. To be used for risk assessment in conjunction with toxicity/effects assessment.
U.S. Environmental Protection Agency. 1993b. "Draft Report: Principles of Neurotoxicity Risk Assessment."	Discusses basics of neurotoxicity and EPA's risk assessment process for neurotoxins. A draft document to be used as guidance; not necessarily Agency policy at present.
U.S. Environmental Protection Agency. 1994f. *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry*.	Describes procedure for the derivation of an inhalation reference dose.

Note: References are listed in shortened format, with complete references given in the reference list following Chapter 10.

DATA SOURCES: Table 5-11 lists sources of health hazard data that should be readily available to most hazard assessors.

TABLE 5-11: SOURCES OF HUMAN HEALTH HAZARDS DATA	
Reference	**Type of Data**
Clayton, G.D. and F.E. Clayton. 1994. *Patty's Industrial Hygiene and Toxicology*.	Toxicology and properties of selected industrial chemicals and classes of chemicals.
Documentation of the Threshold Limit Values and Biological Exposure Indices. UNDATED.	Review of toxicity and rationale for selection of ACGIH exposure levels.

TABLE 5-11: SOURCES OF HUMAN HEALTH HAZARDS DATA

Reference	Type of Data
HSDB®. Hazardous Substances Data Bank (HSDB). Updated Periodically.	An on-line data base that contains information on a chemical's properties, human and environmental toxicity, environmental fate, regulations, and treatments.
International Agency for Research on Cancer (IARC). 1979. *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*.	Reviews the carcinogenicity of chemicals. Provides IARC classification.
International Agency for Research on Cancer (IARC). 1987. *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Overall Evaluations of Carcinogenicity*.	Summary of IARC Monographs, Volumes 1 to 42. Contains rationale for IARC weight-of- evidence classifications.
International Programme on Chemical Safety (IPCS). UNDATED. *Environmental Health Criteria Documents*.	A series of chemical profiles that include information on exposure and toxicity.
National Institute for Occupational Safety and Health (NIOSH). UNDATEDa. *Health Effects Documents*.	Literature review of occupational exposure data, health effects data, and animal studies. Rationale for the derivation of NIOSH exposure levels.
National Institute for Occupational Safety and Health (NIOSH). 1992. *NIOSH Recommendations for Occupational Safety and Health. Compendium of Policy Documents and Statements*.	NIOSH occupational exposure limits.
National Toxicology Program (NTP). UNDATED. *NTP Toxicology and Carcinogenesis Studies*.	Reports results of NTP bioassays for carcinogenicity and chronic toxicity. Provides NTP classification.
U.S. Air Force. 1989. *The Installation Restoration Toxicology Guide, Vols. 1-5*.	Toxicological profiles of hazardous chemicals found at U.S. Air Force sites. In addition to health effects, these documents review properties, regulations, and exposure.
U.S. Department of Health and Human Services. UNDATEDa. *Toxicological Profiles*.	Toxicological profiles of hazardous chemicals most often found at facilities on CERCLA's National Priority List. In addition to health effects and risk levels, these documents review properties, regulations, and exposure.
U.S. Department of Labor, Occupational Safety and Health Administration. 1989a. "Table Z-2. Limits for Air Contaminants."	OSHA occupational exposure limits.

TABLE 5-11: SOURCES OF HUMAN HEALTH HAZARDS DATA	
Reference	**Type of Data**
U.S. Environmental Protection Agency. UNDATEDa. *Drinking Water Regulations and Health Advisories*.	Maximum Contaminant Levels for drinking water (MCLs), Maximum Contaminant Level Goal (MCLGs), drinking water health advisories, and ambient water quality criteria for the protection of human health. MCLs are promulgated pursuant to the Safe Drinking Water Act. MCLG is a non-enforceable concentration of a drinking water contaminant that is protective of adverse human health effects and allows an adequate margin of safety.
U.S. Environmental Protection Agency. UNDATEDb. *Health Assessment Documents (HAD)*.	Reviews of health effects of specific chemicals.
U.S. Environmental Protection Agency. UNDATEDc. *Integrated Risk Information System (IRIS®)*.	Agency position on selected substances, including reviews of selected studies used in the derivation of RfD, RfC, q_1*, and unit risk values. When appropriate data are available, provides EPA classification of carcinogenicity.
U.S. Environmental Protection Agency. 1991d. *Table 302.4. List of Hazardous Substances and Reportable Quantities.*	RQ values for selected hazardous chemicals.

Note: References are listed in shortened format, with complete references given in the reference list following Chapter 10.

The following data bases (Table 5-12) are useful in the absence of other data, but information given should be checked against primary sources for accuracy. The TOXLINE and TOXLIT sources provide abstracts that sometimes contain useful data; most of these data bases are good sources of references to primary literature, such as journal articles.

TABLE 5-12: SUPPLEMENTAL SOURCES OF HUMAN HEALTH HAZARDS DATA	
Reference	**Types of Data**
CANCERLIT®. 1995.	Bibliographic on-line data base containing information on various aspects of cancer.
CCRIS®. Chemical Carcinogenesis Research Information System. 1995.	Factual data bank sponsored by National Cancer Institute. Contains evaluated data and information, derived from both short- and long-term bioassays on 1,200 chemicals.

TABLE 5-12: SUPPLEMENTAL SOURCES OF HUMAN HEALTH HAZARDS DATA

Reference	Types of Data
CHEMID®. Chemical Identification System. 1995.	A chemical dictionary file for over 184,000 compounds of regulatory and biomedical interest. Includes CAS RNs, molecular formulae, generic and trivial names, MeSH headings, and file locators for other files on the ELHILL® and TOXNET® systems. Also provides names and other data used to describe chemicals on over 20 key federal and state regulatory lists.
CHEMLINE®. Chemical Dictionary Online. 1995.	On-line data base that contains 1,142,000 records. Includes chemical names, synonyms, CAS RNs, molecular formulas, National Library of Medicine file locators and, where appropriate, ring structure information.
DART®. Developmental and Reproductive Toxicology. 1995.	Bibliographic data base covering teratology and developmental toxicology literature published since 1989.
EMICBACK®. Environmental Mutagen Information Center Backfile. 1995.	Contains references to chemical, biological, and physical agents that have been tested for genotoxic activity.
ETICBACK®. Environmental Teratology Information Center Backfile. 1995.	Contains references on agents that may cause birth defects.
GENE-TOX®. Genetic Toxicology. 1995.	An on-line data bank created by the EPA as a multi-phase effort to review and evaluate the existing literature and assay systems available in the field of genetic toxicology.
MEDLINE®. MEDLARS Online. 1995.	Bibliographic data base covering medicine, nursing, dentistry, veterinary medicine, and the preclinical sciences. Good source of epidemiological information.
RTECS®. Registry of Toxic Effects of Chemical Substances. 1995.	On-line data base that briefly summarizes the toxicity of a given chemical (not peer-reviewed).
TOXLINE®. 1995	Bibliographic toxicity data base. Abstracts are available.
TOXLIT®. 1995.	Bibliographic data base. Toxicity files from Chemical Abstracts. Abstracts are available.
U.S. Environmental Protection Agency. UNDATEDd. *Health Effects Assessment Summary Tables*.	RfD, RfC, unit risk, and q_1* values for selected chemicals.

Note: References are listed in shortened format, with complete references given in the reference list following Chapter 10.